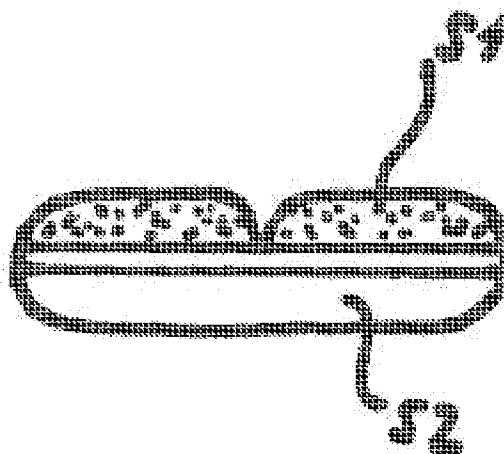


## ENGLISH TRANSLATION OF CH 648754

**Publication number:** CH648754 (A5)  
**Publication date:** 1985-04-15  
**Inventor(s):** HESS HANS DR; VOELLMY CARLO DR +  
**Applicant(s):** CIBA GEIGY AG +  
**Classification:**  
- **international:** A61J3/10; A61K9/20; A61K9/44; A61J3/10; A61K9/20; A61K9/44; (IPC1-7): A61K9/44  
- **European:** A61J3/10; A61K9/20K  
**Application number:** CH19790007514 19790816  
**Priority number(s):** CH19790007514 19790816

### Abstract of CH 648754 (A5)

The pharmaceutical slow release tablet comprises a rod-shaped compressed article which contains a matrix-based slow release tablet composition known per se and one or more active substances which are distributed homogeneously or in longitudinal layers. This compressed article has one or more relatively deep dividing grooves located on one side or both sides in the transverse direction and perpendicular to the smallest diameter. The tablets can easily be divided. The slow release effect of the broken halves is only slightly changed from that of the whole slow release tablet.



Subject-matter of the invention is a divisible pharmaceutical Retard tablet in Stäbchenform.

Pharmaceutical, by-oral dosage forms with delayed active substance delivery for maintenance of constant and prolonged-continuous active substance concentration in the circulation as possible, thus so called Retard forms, are for a long time known, in particular in the form of coated tablets and capsules. More other also ordinary tablets with deep break grooves are as such known and accordingly also certain advantages of the deep break grooves, i.e. easier Brechbarkeit and in the result of precise dosed fractions. In this connection can be referred to the subsequent patent specifications: US 3,883,647, US D 201,497, US D 202467 and DE-AS 1,200 790. Retard-Tabletten, which cannot be broken without substantial loss of the Retard effect into pre-determined uniform parts, as this for ordinary tablets known is, have it up to now given, although a need exists certainly for it.

The pharmaceutical Retard tablet according to invention is characterised in that it from a rod-shaped compact exists, which contains a Retard Tablettenmasse on matrix basis and or of several active ingredients homogeneous or in longitudinal direction schichtweise distributed, which compact in transverse direction and vertical exhibits several in or reciprocally to the smallest diameter or placed, relative deep break grooves.

The depth of the single break grooves or the entire-deep of the reciprocally opposite break grooves amounts to favourable-proves  $\frac{1}{3}$  to  $\frac{1}{2}$ , preferably  $\frac{2}{5}$  to  $\frac{1}{2}$  of the smallest diameter of the Stäbchens. The side surfaces of the break grooves are preferably curved.

The tablet can in or reciprocal biplane or curved and in or reciprocally with opposite or staggered break grooves be provided and can accordingly into two or several pre-determined same or unequal parts decomposed become. This an allowed more individual and thus more exact to be dosedness of the drug depending upon disease picture and patient (adult one in accordance with weight, children, etc.).

The nature of the invention consists of the fact that as small by the special moulding of the present tablet (Stäbchenform with relative deep break grooves) the surface of fracture in the comparison can become the total surface as possible maintained, so that the Retard effect only slight altered will and the weight dispersion of the fractions becomes significantly reduced. Surprisingly became besides found that the reduction of the Retard effect is smaller with the fragments, than actual would have to become expected due to the total surface enlarged around the irregular structured and porous surfaces of fracture. The Retard tablets according to invention have the still subsequent advantages except the major advantages of the light divisibility and the altered Retard effect of the break halves only slight in the comparison to the whole Retard tablet: they are light labeled by embossment or oppression reciprocally, z. B. Manufacturer name on page and trade name and/or a code name of the drug on the other one; they are light sipable, both and whole, and and fragments, i.e. substantial light as round tablets, and/or. their fragments. Also multi-layer tablets with various active ingredients leave themselves and/or. various active substance releases manufacture, whereby certain layers so placed to become to be able that they do not exhibit breaks when breaking.

By additional lateral extension of the break grooves the surface of fracture can be made smaller again, but becomes the tablet thereby to very frangible, whole apart from the manufacture problems, which result from it.

For the preparation of the Retard according to invention tablets the conventional, if necessary on the used active ingredients tuned, adjuvants used can become. From the light Brechbarkeit and the propensity to lids (English: capping) the tablets it results that one preferably proceeds from solid contiguous tablet masses.

The matrix material can be from an actual inert and/or. , z exist indigestible mixture. B. from plastics such as PVC, acrylates and methacrylates. In addition, it can be a material, a progressive softening (z. B.

hydrophilic Gelbildner) or an erosion in the course of the stomach intestine passage is subject (z. B. Lipids in the mixture with inert carrier materials or digestable and triglycerides). Multiple one is also the use of actual retardierenden filling or inertial materials such as z. B. Bentonite, talc, and tricalcium phosphates, lactose, silica, cellulose and. such. simultaneous with the retardierenden materials required or of advantage.

As retardierende materials in detail the subsequent used can become: a) Essential water-insoluble:

Lipids: Fatty alcohols, z. B. Cetyl alcohol, stearyl alcohol, Cetostearylalkohol, Glyceride, z. B. Glycerol monostearate, hydrogenated castor oil, hydrogenated cottonseed oil, mixtures of mono, and triglycerides of vegetable oils; Wax, e.g. Beeswax, carnauba wax; Paraffins, z. B.

Paraffin, earth wax; Fatty acids, e.g. Stearic acid. Cellulose derivatives, z. B. Ethyl cellulose, acetyl cellulose. Polyvinylverbindungen, z. B. PVC, polyvinyl acetate and copolymers with crotonic acid. Polyethylene. Vinyl chloride vinyl acetate of copolymers. Polymers and copolymers and of acrylates and methacrylates, z. B. Copolymers of acrylic acid ethyl ester and methacrylic acid ethyl ester.

b) Water-soluble and/or. with water swellable:

Cellulose derivatives, e.g. Methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethylcellulose, well-carboxymethylcellulose (preferably compounds with higher viscosity). Polyacrylic acid (and salts). Natural (anionic) Schleimstoffe: z. B. Xanthan gum, guar gum, Traganth, alginic acid and salts.

Active ingredients, which are in the neutral intestine environment not particularly good, with the acidic pH of the stomach however better soluble, can be retardiert also with additions, the functional carboxyl groups exhibit (separate in the neutral

rich), z. B. Shellac, cellulose acetatphthalat, Hydroxypropylmethylcellulosephthalat, half ester of maleic anhydride copolymers.

In order to strengthen the tablets according to invention still more other, the compacts can be provided still with a soluble film coat. It should not be however so thick the fact that it make the Brechbarkeit more difficult excessive and simultaneous also steers the release of the active ingredient and/or. significant would affect. The preferred thickness is 20-50 IIm.

Since many active ingredients exhibit an unpleasant bitter taste as well known, the film coat serves also the taste cover. As film coat materials are suitable particularly methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethylcellulose (above all the latter), partially.

in the mixture with talc, wetting agents, pigments (to the ease of the job and/or. to the identification); a mixture of polyvinylpyrrolidone and/or. Copolymer of polyvinylpyrrolidone and polyvinyl acetate with hydroxypropylmethylcellulose, mixtures of shellac with hydroxypropylmethylcellulose or polyvinyl acetate and/or. its copolymers with polyvinylpyrrolidone and mixtures of water-soluble cellulose derivatives (like hydroxypropylmethylcellulose) and water-insoluble ethyl cellulose. These coats become, depending upon solubility of the components, applied in aqueous solution or in organic

solution (mixtures with shellac, ethyl cellulose). Furthermore the subsequent materials can become used: Mixtures of actual water-insoluble Arylaten (z. B. Copolymerisat of acrylic acid ethyl ester and methacrylic acid ethyl ester), which become used in aqueous dispersion, with water-soluble ingredients, z. B. Lactose, polyvinylpyrrolidone, PL glycol.

Hydroxypropylmethylcellulose.

The preparation of the tablet mass can take place via mixing the solid particle (active ingredient and if necessary filler) with retardation means or via mixing already coated active substance particles with ordinary tablet auxiliary materials. The covering can take place in fluidized beds, in Dragierkesseln, in high-speed mixers, in addition, with the help of the method of the microencapsulation.

The preparation of the compacts can with for the preparation of rod-shaped compacts and/or. Multi-layer tablets known pelleting machines take place.

Other objects and advantages of the invention result from the ensuing description in compound with the drawing, the various embodiments explained.

In the figs 1-3 in each case a side view, b is a plan view and a C a break of a tablet according to the invention.

Fig 1 shows a tablet with a single break groove, whereby like the indicated above layer S1 can have another composition than the layer S2. When breaking the tablet the layer remains S1 without fractions. With a combined preparation is z. B. the retardierte active ingredient in layer S1 and the not retardierte in layer S2. With a tablet with only (retardierten) an active ingredient the layer can be S2, also as placebo layer present. The groove depth t e.g. amounts to.  $\frac{1}{3}$  of the height of D of the compact (D = smallest diameter of the compact).

Fig 2 shows a tablet with two single break grooves, corresponding can which be divided into 2 unequal or 3 equal parts. The break grooves can be from same or unequal depths.

Fig 3 shows a tablet with 2 pairs of reciprocally opposite break grooves. Also this tablet can be divided to corresponding into 2 unequal or 3 equal parts. With reciprocally opposite break grooves the weight dispersion of the fractions is smallest. The groove depth t, also the reciprocally opposite grooves can be various. It is z. B. with reciprocally opposite break grooves ever  $\frac{1}{5}$  of the height of D of the compact or entirely  $\frac{1}{3}$  to  $\frac{2}{5}$  of the compact.

#### Example 1

2.0 kg Metoprolol tartrat, 0.1 kg colloidal silicon dioxide, 0.2 kg calcium hydraulic gene phosphate and 0.25 kg microcrystalline cellulose become mixed and with 0,6 kg of an aqueous, 30%-igen dispersion of acrylic acid ethyl ester methacrylic acid ethyl ester 70:30 copolymer in the fluidized bed granulated. The injecting speed amounts to 300 ml per minute, the supply air temperature 30 °C. Subsequent one becomes during 20 minutes with 40 °C supply air temperature in the same Apperatur dried. The granulates becomes into a planet mixer brought and with 0,8 kg molten and on 60 C heated stearyl alcohol staggered and during 15 minutes kneaded. After the cooling the granulates becomes by a screen with mesh 1 mm pressed and in a Taumelmischer with 0,05 kg magnesium stearate, 0.05 kg colloidal silicon dioxide and 0.4 kg of hydroxypropylmethylcellulose viscosity 15,000 cps during 10 minutes mixed.

Injecting this Metoprolol Retardgranulates to tablets zuje 445 mg gross weight the made dimensions subsequent on a round runner tablet press with led punches: Length 17.0 mm, width 8.0 mm. The punches are curved (curvature radius 4.8 mm), and on one of the two are a 2.0 mm deep (related to the Kalottenhöhe) running out break notch (opening angle 45 " 60 ") mounted. The resultant compacts have an height of altogether 4.6 mm.

The coating made in a Dragierkessel of 55 cms diameters, equipped with chicaneries. 5 kg become compacts with a lacquer solution and/or. Suspension, in accordance with subsequent prescription, with the help of a two-material nozzle continuous sprayed.

0.1 kg of hydroxypropylmethylcellulose (viscosity 5 cps) become dissolved in 1,2 kg demineralized water, in addition bottom agitations 0.005 kg polysorbate become 80 and 0.05 kg talc as well as 0.1 kg of a 20%igen homogeneous suspension of titanium dioxide in a solution of 0,007 kg of hydroxypropylmethylcellulose (5 cps) in 90%-igem ethanol given.

The sprayed amount amounts to 19 mg (dry weight) per compact. The supply air temperature amounts to 60 " C, the temperature of the compacts in the kettle becomes on approx. 35 C maintained.

The dissolution rate of the film-coated tablets becomes certain with the diameter method (F.

Prolonged books, H. Rettig, Drug. Dev. Ind. Pharm. 3, 241 [19771), with a flow rate of 16 ml per minute with artificial gastric juice (pH 1.2, without enzymes) during the first hour, subsequent with artificial intestine juice (pH 7.5, without enzymes) with 37 C. For the release of Metoprololtartrat in % of the target content from whole and/or. halved film tablets are the subsequent results typical: Time: whole tablet: halved tablet  
60 min. 23% 27% 120 min. 38% 43% 240 min. 57% 65% 360 min. 72% 78%

Example 2

Retard granulates of Metoprolol tartrat becomes 1 indicated prepared as in example.

Besides a not retardiertes Chlortalidon granulates becomes as follows prepared:

0.25 kg of Chlortalidon, 1.75 kg of lactose and 0.5 kg of corn starch become mixed and with 0,3 kg of a Kleisters from 0,1 kg of corn starch and 0.2 kg of waters in a planet mixer a plastic mass deformed. The wet measures by a screen by 2 mm mesh is driven and in the fluidized bed during 20 minutes with 60 "C dried. , The dried granulates driven by a screen of 1 mm mesh becomes with 0,1 kg talc, 0.01 kg magnesium stearate and 0.29 kg of microcrystalline cellulose mixed.

The grouting of the two granulates made on a round runner tablet machine with led punches, those the preparation of layer tablets allowed. First the retardierte Chlortalidon granulates is metered, subsequent from a second hopper the Metoprolol Retardgranulat. Injecting 2 punches for 2 various break notches with the subsequent dimensions become used: Length 19.0 mm, width 7.0 mm. The curvature radius amounts to 4.2 mm. The running out break notches in the compact have a depth of 1.7 mm (Kalottentiefe), on the page of the Metoprolol layer and of 0.8 mm on the page of the Chlortalidon layer. It results an tablet-high of 6 mm.

The release of Metoprol tartrat made in that bottom examples 1 indicated manner, the decay time of the retardierten Chlortalidon layer amounts to 2-3 minutes (decay testing set after USP, artificial gastric juice with 37).

## CLAIMS

1. Pharmaceutical Retard tablet existing from a rod-shaped compact a contained Retard Tablettenmasse on matrix basis and in or several active ingredients homogeneous or in longitudinal direction schichtweise distributed, which compact in transverse direction and vertical exhibits several in or reciprocally to the smallest diameter or placed relative deep break grooves.
2. Pharmaceutical Retard tablet in accordance with claim 1, characterised in that the depth of the single break grooves or the entire-deep of the reciprocal against over-located break grooves  $\frac{1}{3}$  to  $\frac{2}{3}$ , preferably  $\frac{2}{5}$  to  $\frac{1}{2}$ , the smallest diameter of the Stäbchens amounts to.



